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Modern Concepts of Cardiovascular Disease

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GENETIC FACTORS IN CARDIOVASCULAR DISEASES: I. THE FOUR MAJOR TYPES OF CARDIOVASCULAR DISEASE*†

There is a clinical impression, partially corroborated by statistical and genetic investigations, that heredity plays a role in each of the four major varieties of cardiovascular disease: atherosclerosis, including coronary artery disease; hypertension; rheumatic fever, and therefore rheumatic heart disease; and congenital malformations of the cardiovascular system.

It is important to appreciate the multiple influences that enter into the cause of each of these forms of heart disease. Heredity cannot be said to be *the* cause of any, just as it is not possible to say that diet, stress, physical inactivity or cigarette smoking is *the* cause of coronary artery disease. To insist that there is a genetic factor in coronary artery disease does not deny the importance of other factors, just as to hold there is a genetic factor in the susceptibility to rheumatic fever does not deny the paramount importance of the streptococcus. In pointing out a genetic factor in some congenital malformations of the heart, one need not underrate the importance, in the same or other cases, of nongenetic factors operating in the intra-uterine environment, of which maternal rubella is the clearest example.

The reasons that analysis of genetic factors is of importance are at least two: (1) potentially it will permit recognition of genetically susceptible individuals for more efficient and economical application of preventive measures; (2) from knowledge of the mechanism by which the genes determine increased vulnerability will come methods for breaking the chain leading to disease.

In addition to the four major forms of cardiovascular disease in which genetic factors play a supporting role in pathogenesis, there are numerous rarer and more strictly genetic disorders in which the cardiovascular system is significantly involved. These will be reviewed in Part II of this article, appearing in the next issue.

ATHEROSCLEROSIS, WITH PARTICULAR REFERENCE TO CORONARY ARTERY DISEASE

Evidence bearing on genetic factors in coronary artery disease is provided by the following: (1) family studies, (2) twin studies, (3) studies of body build, (4) lipid studies and (5) ethnic studies. In most of these areas, data are limited and observations are susceptible to various interpretations.

Family studies, focusing on clinical coronary artery disease, by Gertler and White,[1] Russek,[2] Thomas and Cohen,[3] and others, indicate a familial aggregation of these cases. Nongenetic factors could, of course, account for these results when taken alone. There are few twin studies using clinical coronary artery disease as the trait[4] and these are limited in scope. With some exceptions,[5] they yield results consistent with the hypothesis of a significant genetic factor. Although there is no pathognomonic "coronary habitus," young coronary artery victims as a group have been found to differ from a control group with respect to body build, there being, specifically, a deficiency of ectomorphs in the coronary group.[1]

Granting that hypercholesteremia and hyperlipemia predispose to coronary artery disease—and in the opinion of the reviewer such is adequately established—one can use the data on the

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† Part II of this article, concerned with less frequent disorders of primarily genetic etiology, will appear in the August issue.

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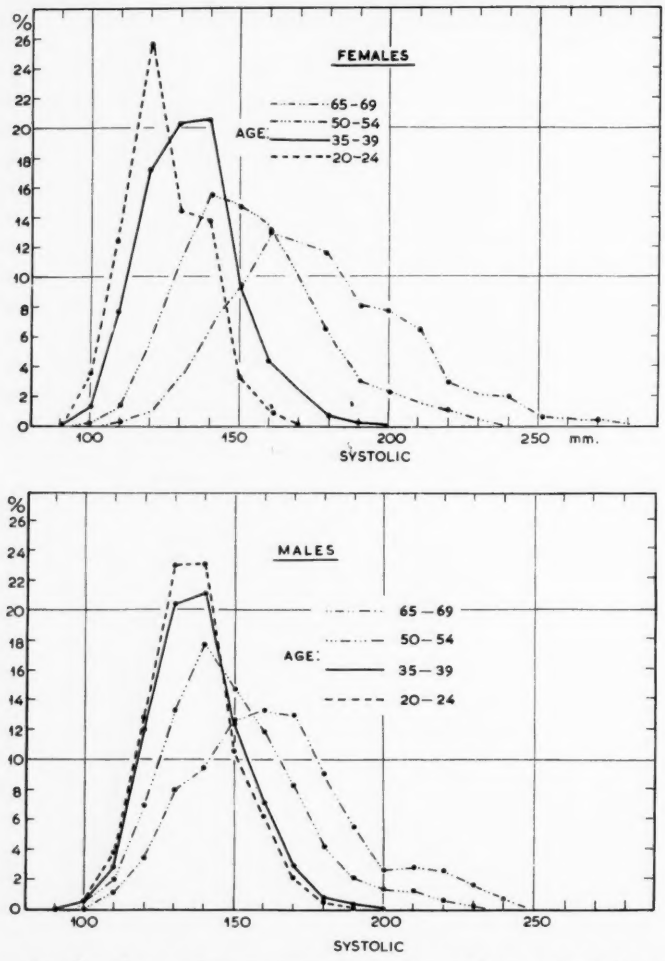

Figure 1. These data from Bøe, *et al.*,[22] are representative of several large studies indicating that blood pressure in the population in each age group falls on a curve which is essentially normal.

genetic control of lipid metabolism as strong evidence for genetic factors in the pathogenesis of coronary artery disease. Not only the pronounced forms of deranged lipid metabolism (see below) but the lesser grades of hypercholesteremia are under partial genetic control. Excellent studies[6] of monozygotic and dizygotic twins and of monozygotic twins living together and apart, demonstrate the operation of both environmental and genetic factors. The distribution of cases of hypercholesteremia within families follows the pattern expected of a genetic influence[7] and would be inexplicable if diet, for example, were the only determining factor.

Differences among ethnic groups must be interpreted with great caution because their environments may not be comparable. In New York City, Epstein and colleagues[8] found over twice as high a rate for coronary artery disease in Jewish as in Italian garment workers. Dietary differences seemed to be an inadequate explanation for this difference and no other than a genetic one was evident. There was a parallel difference in serum cholesterol in the two groups.[9] Adlersberg and his colleagues[7] found hypercholesteremia over twice as often in Jews as in non-Jews seen as patients at the Mt. Sinai Hospital in New York. The incidence of hypercholesteremia in members of the families of hypercholesteremic Jews was the same as that in the families of hypercholesteremic non-Jews—a fact arguing against dietary influences as the basis for the differences in serum cholesterol.

By what means does genetic make-up deter-

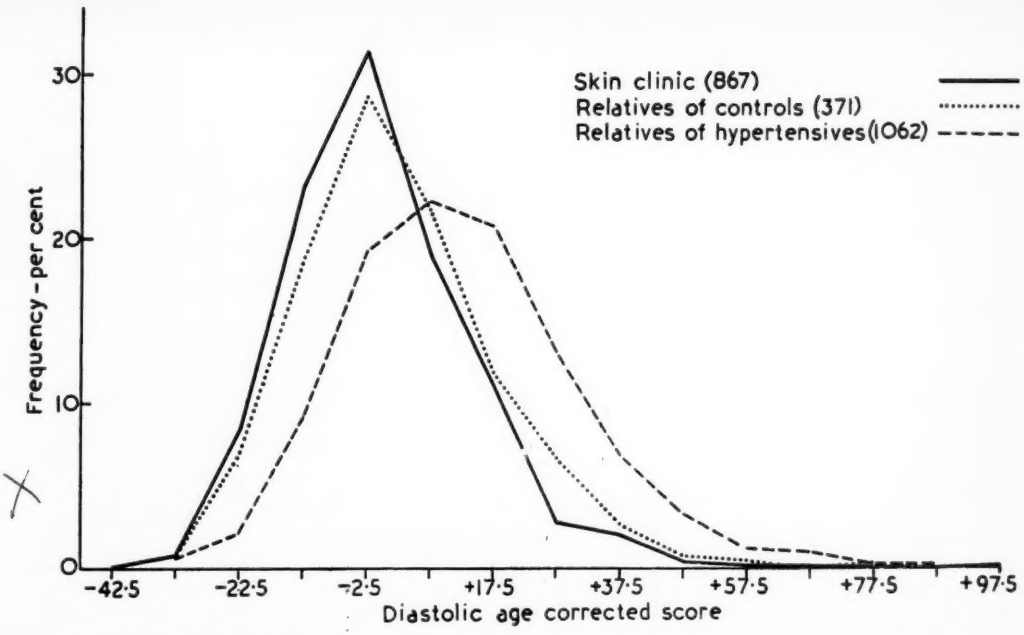

Figure 2. The distribution of diastolic blood pressure score (correcting for age and sex) in controls (patients of the skin clinic), relatives of controls, and relatives of hypertensives. From Hamilton, Pickering, Roberts and Sowry.[20]

mine susceptibility to coronary artery disease? Lipid metabolism is an obvious mechanism, as already noted. Probably the susceptibility of diabetics to coronary artery disease is mainly on this basis. Diabetes mellitus is an inborn error of metabolism, but its genetic background has not been fully clarified. Hypertension (see later) aggravates generalized arteriosclerosis and is frequently associated with coronary artery disease.

Genetically determined differences in the anatomy of the coronary arterial tree might account for its increased vulnerability to the effects of atherosclerosis. Direct evidence on familial similarities in coronary anatomy is not available and obviously is difficult to obtain. Demonstrations of the hereditary basis of other vascular patterns in man, such as that of the anterior chest wall, the antecubital fossa, the aortic arch, and the hand of the fetus, provide a precedent. In man, three patterns of major branching have been identified:[10] (1) right coronary artery predominant; (2) balanced coronary artery pattern; and (3) left coronary artery predominant. Hearts with the third type are most vulnerable to fatal coronary occlusion and those of the second type are least vulnerable. Furthermore, intercoronary anastomoses[11] vary in animals. In man,[12] the extent of intercoronary anastomoses is thought to be genetically determined.

Temperament and personality pattern, characters of partial genetic determination, have received increasing attention in connection with the pathogenesis of coronary artery disease.

Special Aspects

It is uncertain whether so-called *idiopathic hypercholesteremia* is a discrete entity or merely the upper end of a bell-shaped distribution curve for the level of serum cholesterol. In the latter view, serum cholesterol is a graded character like height or blood pressure (see later), and the inheritance probably, although perhaps not necessarily, is polygenic. Defining hypercholesteremia arbitrarily, several investigators[13-15] have suggested unifactorial inheritance of the autosomal (non-sex-linked) dominant type. Some[13] maintain that the gene must be present in the homozygous state for the development of xanthomata of the skin and tendons and for an increase in the incidence of atherosclerosis. Others[14, 15] think the heterozygous state suffices, although deposits are increased if the homozygous state obtains.

Idiopathic hyperlipemia is distinguished from idiopathic hypercholesteremia by the presence of lactescence of the fasting serum. Xanthelasmata and xanthomata of the Achilles, patellar and olecranon tendons occur more rarely than in hypercholesteremia, although xanthomata of the extensor tendons of the fingers and of the skin

(xanthoma tuberosum) do occur.[16] Atherosclerosis develops prematurely[17, 18] as in hypercholesteremia. Boggs, *et al.*,[18] suggest that the inheritance is that of an autosomal recessive. Milder derangements of lipid metabolism have been demonstrated in the parents and siblings of affected persons.[18] These individuals may be "heterozygotes" with respect to the trait.

A variety of arteriosclerosis affecting both peripheral arteries and the coronary arteries occurs with *pseudoxanthoma elasticum*, a heritable disorder of connective tissue (see Part II). Furthermore, heavy intimal deposits of mucopolysaccharide occur in children with the *Hurler syndrome* (gargoylism), producing clinical and pathological simulation of ordinary atherosclerosis.

HYPERTENSION

What is hypertension? Pickering and his colleagues[19-21] have proposed an answer to this question which has reoriented research in the genetics of hypertension. It is the conclusion of this group that blood pressure is a continuous variable like height* and that what we term "essential hypertension" is merely an arbitrary truncation of the upper end of a bell-shaped distribution curve for blood pressure (see Figures 1 and 2). In this view, it is not essential hypertension as a disease which is inherited but rather level of blood pressure.

The evidence for genetic control of blood pressure and the inheritance of hypertension is derived from several sources: (1) family studies, (2) twin studies, (3) ethnic studies, (4) the cold pressor test and (5) an animal analogue. Family studies[27-29] have demonstrated an aggregation for cerebral apoplexy and hypertensive cardiovascular-renal disease. The proportion of siblings affected by hypertension and its complications differs according to whether neither parent, one parent, or both parents have had the condition. These observations strengthen the genetic hypothesis.

When the blood pressure in first degree relatives (parents, siblings, and children) is compared with the blood pressure of the index case (propositus) by the use of a scoring technique to account for the sex differences in blood pressure and the "growth" of blood pressure with age,[30] a significant difference is found between relatives of hypertensive patients and relatives of controls by Pickering's group[20] (Figure 2). A significant correlation between the blood pressure scores of propositi and those of their relatives was found by Miall and Oldham:[16, 25] a regression coefficient of 0.224 ± 0.022 (between propositi and first degree relatives) was found for systolic pressure (Figure 3).[25] This means that if the index case has a systolic blood pres-

* Similar evidence is provided by Bøe, *et al.*, in Bergen,[22] Comstock in Georgia,[23] Master, Garfield and Walters in New York,[24] Miall and Oldham in Wales,[25] Gover in rural United States,[26] and others.

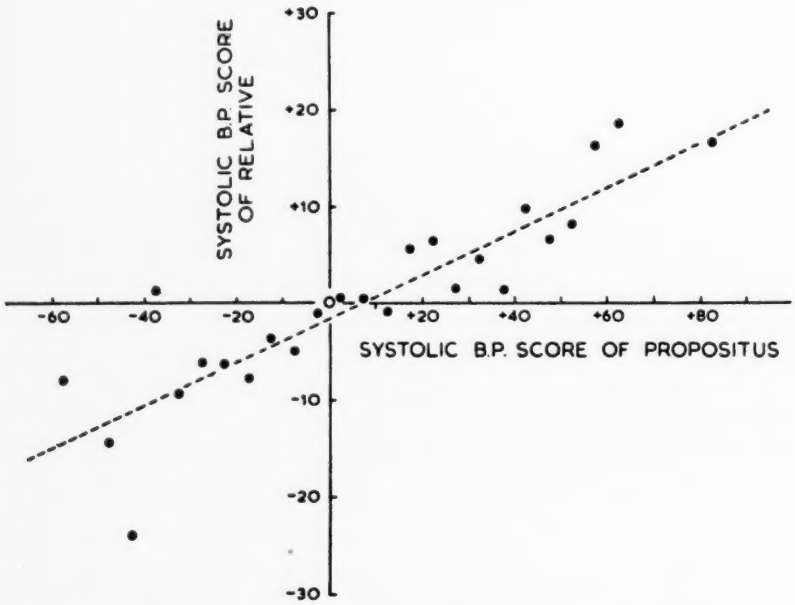

Figure 3. The relationship between the systolic blood pressure scores of propositi and the mean systolic scores of relatives. From Miall and Oldham: Acta Genet. et Statist. Med. **7**: 114, 1957.[25]

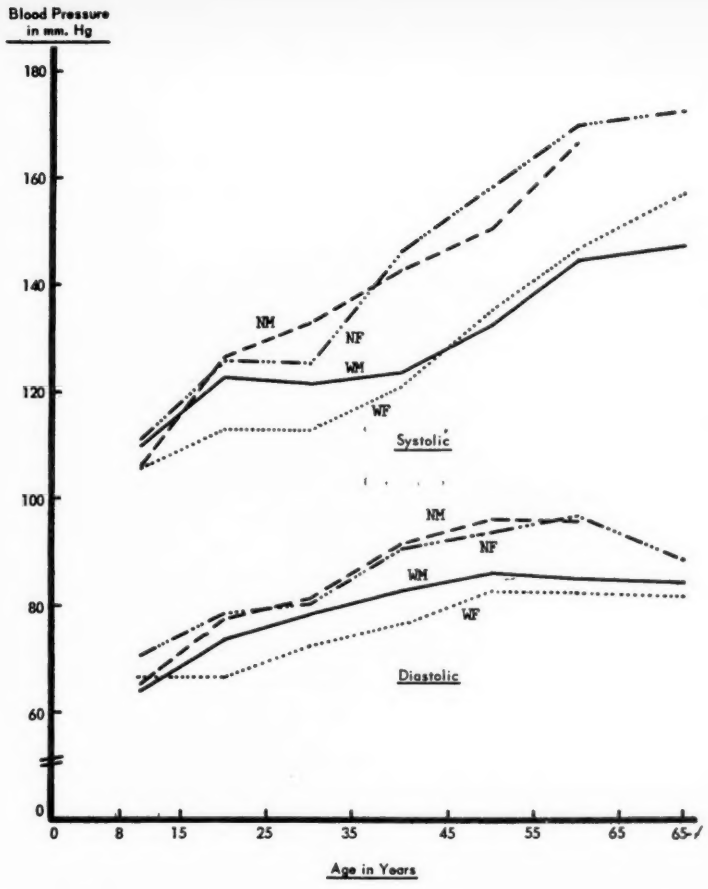

Figure 4. Mean systolic and diastolic blood for negro males (NM), negro females (NF), white males (WM) and white females (WF). From Comstock.[23] Data collected on large sample in Muscogee County, Georgia.

sure score of 50 mm. Hg in excess of the mean, the average systolic score for his first degree relatives can be expected to be 11-12 mm. above the average. If blood pressure were entirely genetic in its determination, the regression coefficient would be 0.50[31] because the genetic resemblance of first degree relatives is 0.50 on a scale in which 1.0 is the genetic resemblance of identical twins and the genetic resemblance of unrelated individuals approaches 0.

Twin studies reveal closer similarities of blood pressure in monozygotic twins than in dizygotic twins of the same sex.[32] Twin studies, using complications of hypertension as the trait for analysis, also support the genetic hypothesis.[33]

The American Negro (Figure 4), has a blood pressure which is, on the average, higher for all ages and for both sexes[23] than that of his white contemporaries. In the interpretation of these ethnic data, the same caution mentioned earlier must be exercised.

Strains of rabbits with high blood pressure have been studied by Alexander, Tibbs and Drury.[34]

There appear to be family resemblances in regard to hyperreactivity to the cold pressor test.[35] Hypertension may be more likely to develop in hyperreactors,[36] although some[37] have questioned this conclusion.

A corollary of the conclusion that blood pressure is a continuous variable is the view that it is multifactorial in its genetic determination. Like height, blood pressure (including hypertension) is not susceptible to genetic interpretation as a "dominant" or "recessive."

As a footnote, one may mention the special genetics of two forms of hypertensive disease. Humphries[38] finds that the mothers of women with *hypertensive toxemia of pregnancy* had hypertensive toxemia over 2½ times as often as the mothers of nonhypertensive pregnant women. Additional information on the mother-daughter

Table I

Frequency of Congenital Heart Disease in Siblings of 1188 Patients with Congenital Heart Disease (From Lamy, et al.[52])

	Classes (defined below)								
	I	II	III	IV	V	VI	VII	VIII	Total
Number of propositi	238	56	136	143	97	54	332	132	1188
Number of siblings	404	107	249	213	161	78	594	239	2045
Number of siblings with CHD	4	4	3	1	2	2	13	1	30
Per cent of siblings with CHD	1.0	3.74	1.2	0.47	1.24	2.58	2.19	0.42	1.46

I. Tetralogy of Fallot with or without ASD.
II. Pure pulmonary stenosis, with or without ASD.
III. Patent ductus arteriosus, with or without other defect.
IV. Ventricular septal defect.
V. Atrial septal defect (ASD).
VI. Coarctation of aorta.
VII. Undiagnosed, or highly complex.
VIII. Miscellaneous, individually uncommon defects.

Controls: No congenital heart disease among 1483 children in 660 sibships. (Others[53] place the frequency of congenital heart disease at the age of 10 years at about 0.1 per cent.)

pairs suggested that hypertension in pregnancy may be only part of a familial tendency to hypertension. Multiple cases of *pheochromocytoma* occur in families.[39] In some, pheochromocytoma is merely one facet of von Recklinghausen's neurofibromatosis, which is inherited as an autosomal dominant. In 1950 Davis, *et al.*,[40] found descriptions of associated neurofibromatosis in 10 of the 203 recorded cases of pheochromocytoma.

RHEUMATIC HEART DISEASE

Susceptibility to rheumatic fever may, according to evidence from the following sources, be genetically determined to a significant degree by: (1) family studies, (2) twin studies and (3) studies of physical characteristics. A concentration of cases of rheumatic fever in families has been found in large studies conducted in Baltimore,[41] New York City,[42] New Haven,[43] Toronto,[44] Belfast,[45] Chicago[46] and elsewhere. By itself, such familial aggregation is unsatisfactory evidence for genetic predisposition. However, the difference in the proportion of affected siblings according to its occurrence in the parent generation, *i.e.*, whether neither parent, one parent, or both parents had had rheumatic fever, seems explicable only on genetic grounds. Almost all workers have concluded from family studies that there is a genetic factor in predisposition. Wilson, and her colleagues,[42] have gone further to suggest that the genetic predisposition is inherited as an autosomal recessive. Application of the Lenz-Hogben method of analysis and use of simple mendelian ratios for estimating the proportion of affected siblings to be expected among offspring from matings of different types with respect to rheumatic fever, seem to support the recessive hypothesis. Some family studies of rheumatoid arthritis have revealed an increased incidence of rheumatic fever in the same families.[47]

A significantly increased concordance for rheumatic fever in monozygotic twins has been reported several times.

Clinical experience has suggested to some the existence of a "rheumatic fever type"—for example, a child with fair, freckled complexion and reddish hair. Paul[48] reviewed several studies of physical characteristics in victims of rheumatic fever and concluded as follows: "Measurements [in this area] are so difficult and the data in the literature so conflicting that it would seem unwise to pursue this subject beyond mentioning that the hypothesis has proponents."

CONGENITAL MALFORMATIONS

Until recently, the only suggestion of genetic factors in the common varieties of congenital malformation has been that provided by the occasional reports of single families with more than one affected member. In most, it was a matter of multiple affected siblings. In the case of coarctation,[49] patent ductus arteriosus,[50] aortic stenosis,[50] and atrial septal defect,[51] affected members in successive generations sometimes have been observed.

Recent evidence on genetic factors has been of these types: (1) familial aggregation in sizable controlled series, (2) consanguinity studies, (3) twin studies and (4) an animal analogue. Several studies,[52, 53] of which the data in Table I are illustrative, indicate an increase in congenital malformations of the heart in the brothers and sisters of affected propositi as compared with controls. Also, there is probably an increased incidence of congenital heart malformations in the first cousins of propositi.[52] For the "garden varieties" of malformation, the increased risk in subsequent pregnancies is, however, still not great—less than 4.0 per cent for pure pulmonary stenosis from the data of Lamy, *et al.*[52] For the common types of malformations, and excluding mongolism (see below), the risk is scarcely large enough to warrant restriction of further childbearing after the birth of one affected child.

The common forms of congenital cardiac malformations clearly do not display a pattern of inheritance consistent with a "dominant" or a "recessive" trait. Inheritance is probably polygenic. Nothing is contributed by the occasional report of families with multiple affected sibs in which the inheritance is said to be that of a simple recessive or of families with successive affected generations in which inheritance is said to be that of a simple dominant. Such families are selected from among many. With an average familial aggregation of 3 per cent in sibs one must expect occasional families of the type indicated to occur by chance alone.

Consanguinity—recognized blood relationship—is observed more often in the parents of patients with congenital heart disease than in the general population.[52, 53]

Studies of congenital heart disease in twins suggest a relatively weak genetic factor of the low order of magnitude suggested by the other data reviewed above. Numerous pairs of monozygotic twins with only one affected by congenital heart disease have been reported[54, 55] and rather few instances in which both twins were affected. In part, the low rate of concordance in monozygotic twins may be due to a "loading" of twin series by cases in which the congenital malformation in one twin resulted from *in utero* competition for blood supply.[56] This hypothesis may require, however, that congenital heart disease is more common in twins than in the singly born.

Siller[57] has studied ventricular septal defect in the domestic fowl. The inheritance is probably polygenic.

Special Forms of Congenital Malformation

Endocardial fibroelastosis, especially that occurring as an isolated abnormality, has several times been described in multiple siblings and in both of identical twins.[58]

Possibly as many as 40 per cent of all *mongoloid idiots* have a congenital cardiac malformation, most often AV communis.[59] In the pathogenesis of mongolism, a collaboration of genetic factors and higher maternal age seems likely.[60] It is now established[61, 62] that the fundamental error in mongolism is the presence of an extra autosomal (nonsex) chromosome, due apparently to "nondisjunction" of one chromosome pair during maternal gametogenesis. Nondisfunction may be more likely to occur in older mothers and in mothers with a particular genetic constitution.

In the *Turner syndrome*, coarctation of the aorta is associated with gonadal dysgenesis, dwarfism and webbed neck.[63] Although phenotypically female, most cases are "chromatin-negative," *i.e.*, "male" by the Barr technique. There are a few reports of multiple affected siblings,[64, 65] but the frequency of these is not enough to suggest a clear-cut genetic basis. It is now known that a chromosomal aberration is the basic error.[66] Cases of the Turner syndrome have only one sex chromosome and are designated "XO." The presence of only one X chromosome results in "chromatin-negativity"; the absence of a Y chromosome results in development of female genitalia. (Interestingly, hypertension occurs in a significant number even in the absence of coarctation and a puzzling angiomatosis of the bowel leading to gastrointestinal bleeding is found fairly often.[63]) Coarctation of the aorta is sometimes associated with webbed neck (pterygium colli), short stature and short fingers without gonadal dysgenesis—the Bonnevie-Ullrich syndrome.

In the *Ellis-van Creveld syndrome*,[67] the features of note are: (1) chondrodystrophy, (2) polydactylism and (3) congenital malformation of the heart, usually single atrium. Inherited as an autosomal recessive,[68] it is one of the rarest of hereditary states, occurring, according to indirect estimates[69] based on the rate of parental consanguinity, only once in four million persons!

In the *Kartagener syndrome*, bronchiectasis and malformation of the paranasal sinuses are associated with dextrocardia and situs inversus of the other viscera.[70, 71] Although it is clearly hereditary, the mode of inheritance has not been worked out satisfactorily. *Situs inversus viscerum*

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has a genetic background, at least in part, although the genetics is probably[72] more complex than that of a simple recessive, as suggested by Cockayne. Major cardiovascular malformation occurs much less often with situs inversus viscerum than with isolated dextrocardia. The latter has no particular genetic determination.

Methemoglobinemia[73] and *sulfhemoglobinemia*[74] are in some instances hereditary conditions which result in multiple "blue babies" in families. Mention is made of these only because they are conditions which tend to turn up in cardiac clinics. Gasul, *et al.*,[75] had a case of methemoglobinemia simulating tricuspid atresia.

The Marfan syndrome will be discussed in the following section, because it is clear that the predominant cardiovascular manifestations are not congenital malformations in the conventional sense.

(To be concluded)

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REFERENCES

Space does not permit the publication of the references included in Parts I and II of this article. A complete list of references is available, on request, from the *Author* or from the *Membership Section of the American Heart Association.*

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